Mortality risk among hemodialysis patients receiving different vitamin D analogs

Kidney International (2007) **72,** 895; doi:10.1038/sj.ki.5002335

To the Editor: Tentori *et al.*[1] reported a 20% increased risk of mortality in dialysis patients who were not taking intravenous vitamin D compared to those who received vitamin D, confirming studies showing a survival benefit in patients administered vitamin D.[2–4] However, Tentori *et al.* claim there was no differences in mortality risk when comparing the use of calcitriol (1α,25-dihydroxyvitamin D_3) with doxercalciferol (1α-hydroxyvitamin D_2) and paricalcitol (19-nor-1α,25-dihydroxyvitamin D_2). Unfortunately, there are significant limitations with their analyses, and subsequent conclusions. The authors have taken liberty in their claim of 'equivalency' between doxercalciferol and paricalcitol and in their comparison to previous studies that employed larger databases and longer treatment periods.[2–4]

It is unclear if the authors understand the differences between the various vitamin D compounds. Although both paricalcitol and doxercalciferol are D_2, whereas calcitriol is a D_3 compound, the major differentiating factor in the activation of the vitamin D receptor (VDR) is that paricalcitol has a modification in the A ring. In fact, doxercalciferol is an inactive pro-hormone that has to be converted by the liver to its active form (1α,25-dihydroxyvitamin D_2) and it is unclear if there are differences in the activation of the VDR by 1α,25-D_3 or 1α,25-D_2. Thus, it is misleading when the authors equate paricalcitol and doxercalciferol by referring to them collectively as D_2 compounds.

Important limitations of this study include the relatively small number of patients and the fact that the treatments were not simultaneous but sequential and short in duration. There were 7731 patients who received vitamin D at any time and the median observation period was less than 10 months. Patients who received calcitriol started sooner after initiating dialysis, were not dosed according to KDOQI guidelines and were started on therapy earlier in the study period than those receiving other compounds, whereas those who received doxercalciferol had the shortest follow-up and were started on therapy later in the study period. Moreover, only about 50% of the treated patients received vitamin D for more than 6 months. The high rate of censoring was largely due to patients being switched from one D compound to another (38%). It is likely that the study was underpowered to show a 12–16% survival difference between calcitriol and paricalcitol as was demonstrated by Teng *et al.* after evaluation of 67 399 patients.[2]

On the basis of these limitations, the authors should acknowledge that they were unable to show survival differences among the vitamin D treatment groups in large part because the study was underpowered and the design was not appropriate to make a statement of equivalence. This would be a fairer interpretation of their data than the inappropriate claim that the major finding of the study was the lack of a survival difference between paricalcitol and doxercalciferol. In addition to the impact on patient care, there is an enormous financial stake associated with the use of these compounds. Thus, before coming to conclusions regarding the effect of vitamin D in general and the relative effect of different compounds in particular, appropriately designed and powered studies are required to determine the best practice for reducing mortality associated with chronic kidney disease.

1. Tentori F, Hunt WC, Stidley CA *et al.* Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; **70**: 1858–1865.
2. Teng M, Wolf M, Lowrie E *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; **349**: 446–456.
3. Teng M, Wolf M, Ofsthun MN *et al.* Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol* 2005; **16**: 1115–1125.
4. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; **70**: 771–780.

SM Sprague[1]
[1]*Northwestern University Feinberg School of Medicine, Evanston Northwestern Healthcare, Evanston, Illinois, USA*
Correspondence: *SM Sprague, Northwestern University Feinberg School of Medicine, Evanston Northwestern Healthcare, 2650 North Ridge, Evanston, Ilinois 60201, USA. E-mail: ssprague@northwestern.edu*

Response to 'Mortality risk among hemodialysis patients receiving different vitamin D analogs'

Kidney International (2007) **72,** 895–896; doi:10.1038/sj.ki.5002360

We appreciate Dr Sprague's letter[1] to our article.[2] Doxercalciferol undergoes hepatic conversion to its active form (1,25-dihydroxyvitamin D_2), but once activated, it is a vitamin D_2 analog.

Dialysis Clinic Inc. (DCI) is a large not-for-profit provider. Procedural differences between DCI and for-profit providers may influence clinical outcomes. The use of an incident versus a prevalent cohort reduced our sample size and the impact of potential confounders. The crude mortality rate (deaths/100 patient years, 95% confidence interval (CI)) was higher among patients receiving calcitriol (19.6, 18.2–21.1) versus paricalcitol (15.3, 13.6–16.9) ($P<0.0001$) or doxercalciferol (15.4, 13.6–17.1) ($P=0.0003$). However, in our Cox models, administration of paricalcitol and doxercalciferol versus calcitriol was associated with a survival benefit only in the unadjusted model and the model adjusted for demographics, reflecting our relatively small sample. Never-

theless, in our fully adjusted model, the 95% CI for the hazard ratio associated with the administration of paricalcitol versus calcitriol included the point estimate reported by Teng *et al.*[3] Paricalcitol appears to confer no survival advantage over doxercalciferol. The point estimates for hazard ratios for doxercalciferol versus paricalcitol ranged from 0.99 to 1.06 and each 95% CI included 1.0. However, we cannot exclude the possibility that doxercalciferol may be associated with a small benefit or disadvantage over paracalciferol.

Our retrospective study reflects clinical practice. Since different vitamin D preparations became available at different times, the treatments were not simultaneous, and switching was the major cause of censoring. The vitamin D analogs were not dosed according to KDOQI guidelines, since most of the study occurred before these were published.

1. Sprague SM. Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; in press.
2. Tentori F, Hunt WC, Stidley CA *et al.* Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; **70**: 1858–1865.
3. Teng M, Wolf M, Ofsthun MN *et al.* Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol* 2005; **16**: 1115–1125.

F Tentori[1], WC Hunt[1], CA Stidley[1], MR Rohrscheib[1], EJ Bedrick[1], KB Meyer[1], HK Johnson[1] and PG Zager[1]

[1]*Dialysis Clinic Inc. (DCI), Quality Management, Albuquerque, New Mexico, USA*

Correspondence: *F Tentori, Dialysis Clinic Inc., Quality Management, 1500 Indian School Rd NE, Suite 200, Albuquerque, New Mexico 87102, USA.*
E-mail: francesca.tentori@dciinc.org

Immunofluorescence on proteinase XXIV-digested paraffin sections

Kidney International (2007) **72,** 896; doi:10.1038/sj.ki.5002495

To the Editor: In their comparison of immunofluorescence (IF) on frozen sections with pronase-digested paraffin sections, Nasr *et al.*[1] found that pronase digestion was a useful technique for IF on paraffin (IF-P) sections. However, the sensitivity of this technique was low for membranous glomerulopathy and anti-glomerular basement membrane disease (50 and 20%, respectively), which was mainly due to weak staining of IgG (immunoglobulin G).

In our laboratory, we use bacterial proteinase XXIV (Sigma, St Louis, MO, USA), as described by Bancroft and Gamble,[2] instead of pronase. We compared IF-P on proteinase XXIV- and pronase-digested paraffin sections. We selected five cases of lupus nephritis that showed full-house fluorescence staining on frozen sections. In all cases, staining intensity was similar or better on proteinase XXIV-digested slides, and less background was observed. Importantly, staining for IgG and C1q was more intense in sections digested with proteinase XXIV than in those digested with pronase. In addition, we tested five cases of anti-glomerular basement membrane disease. One of these was negative after pronase, as well as after proteinase XXIV digestion, one was positive with both techniques, whereas the remaining three were positive only after proteinase XXIV digestion. Finally, in nine cases of membranous glomerulopathy, diagnostic IF-P staining for IgG was obtained in six cases after pronase digestion and in five cases after proteinase XXIV digestion.

In conclusion, we agree with Nasr *et al.* that IF-P is a valuable salvage technique for renal biopsies. To this, we would like to add that IF-P on sections digested with proteinase XXIV is generally more sensitive than IF-P on pronase-digested sections.

1. Nasr SH, Galgano SJ, Markowitz GS *et al.* Immunofluorescence on pronase-digested paraffin sections: a valuable salvage technique for renal biopsies. *Kidney Int* 2006; **70**: 2148–2151.
2. Bancroft JD, Gamble M. *Theory and Practice of Histological Techniques*, 5th edn. Churchill Livingstone, London, 2002, pp 450–451.

K van der Ven[1], TQ Nguyen[1] and R Goldschmeding[1]

[1]*Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands*

Correspondence: *R Goldschmeding, Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands.*
E-mail: R.Goldschmeding@umcutrecht.nl

Machiavelli and urinalysis

Kidney International (2007) **72,** 896–897; doi:10.1038/sj.ki.5002496

To the Editor: I read with great interest the article on the history of urinalysis in Western culture by Armstrong.[1] It gives a detailed outline of how uroscopy developed into a prominent medical diagnostic tool, and later was abandoned due to the poor scientific basis of such practice. In Dr Amrstrong's article, however, it is not mentioned that uroscopy was so popular to be included in the most famous play by Niccolò Machiavelli, 'La Mandragola (The Mandrake)',[2,3] making fun of presumptuous physicians and credulous patients. In another important paper on uroscopy by Voswinckel,[4] the contribution of Machiavelli is not mentioned as well.

Niccolò di Bernardo dei Machiavelli (May 3, 1469 to June 21, 1527) was an Italian political philosopher. He is a central figure of the political component of the Italian Renaissance, most widely known for his treatises on realist political theory (*The Prince*). However, he also was a musician, poet, and romantic comedic playwright.

The Mandragola has been widely performed and very popular since the sixteenth century. The title comes from the popular tale that a woman who drinks a potion made from the mandrake root is certain to conceive a child, the only drawback being that the man with whom she first has sex after taking the potion will die within 8 days. The story evolves around Callimaco, a lovesick Florentine who came form Paris to conquer the heart (and the graces) of Lucrezia, the beautiful young wife of Messer Nicia Calfucci, a